

NDA 20-412/S-013
NDA 20-413/S-005

SEP 27 2000

Bristol-Myers Squibb Company
Attention: Cynthia F. Piccirillo
Associate Director, Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Piccirillo:

Please refer to your supplemental new drug applications dated August 23, 1999, received August 24, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZERIT® (stavudine) Capsules and Pediatric Oral Solution (POS).

We acknowledge receipt of your submissions dated:

August 23, 1999

December 6, 1999

May 9, 2000

July 20, 2000

August 14, 2000

These supplemental new drug applications provide for the addition of a Geriatric Use section of the ZERIT® (stavudine) label, as follows:

Clinical studies of ZERIT did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Greater sensitivity of some older individuals to the effects of ZERIT cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ZERIT is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see DOSAGE AND ADMINISTRATION: Dosage Adjustment).

These supplemental new drug applications additionally provide for the addition of important new safety information to the ZERIT® (stavudine) label, to include changes to the **Black Boxed Warnings, WARNINGS, and PRECAUTIONS: Information for Patients** sections, to include warnings regarding death due to hepatotoxicity and/or pancreatitis when ZERIT is used in regimens containing didanosine and hydroxyurea, as follows:

Black Boxed Warnings:

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN ZERIT WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

WARNINGS**1: Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure:**

An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea compared to when ZERIT is used alone. Patients treated with this combination should be closely monitored for signs of liver toxicity.

WARNINGS**3: Pancreatitis:**

Fatal and nonfatal pancreatitis have occurred during therapy when ZERIT was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of ZERIT and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of ZERIT after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS: Information for Patients:

Patients should be informed that when ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Finally, these supplemental new drug applications also provide for the addition of a revised **PRECAUTIONS: Nursing Mothers** section, as follows:

The Centers for Disease Control and Prevention recommend that HI V-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving ZERIT.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that drug products are safe and effective for use as recommended in the agreed upon labeling text, submitted August 14, 2000. Accordingly, the supplemental new drug applications are approved effective on the date of this letter.

The final printed labeling must be identical to the submitted labeling (package insert submitted August 14,2000, and patient package insert submitted August 14,2000). Marketing the product(s) with Final Printed Labeling (FPL) that is not identical to the approved labeling text may render the products misbranded and an unapproved new drug

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed, to each application. Please mount individually ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format*- NDAs (January 1999). For administrative purposes these submissions should be designated "FPL for approved supplement NDA 20-412/S-013, NDA 20-413/S-006." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., an "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Destry M. Sullivan, MS, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ZERIT® (stavudine)

ZERIT® (stavudine) Capsules

ZERIT® (stavudine) for Oral Solution

(Patient Information Leaflet Included)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN ZERIT WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

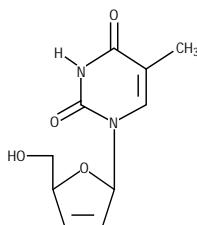
DESCRIPTION

ZERIT® is the brand name for stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the Human Immunodeficiency Virus (HIV).

ZERIT (stavudine) Capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

ZERIT (stavudine) for Oral Solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL of a 1 mg/mL stavudine solution upon constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.

MICROBIOLOGY

Mechanism of Action: Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate ($K_i = 0.0083$ to $0.032 \mu M$), and by its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3'-OH group. Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

***In Vitro* HIV Susceptibility:** The *in vitro* antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit viral replication by 50% (ED_{50}) ranged from 0.009 to $4 \mu M$ against laboratory and clinical isolates of HIV-1. Stavudine had additive and synergistic activity in combination with didanosine and zalcitabine, respectively, *in vitro*. Stavudine combined with zidovudine had additive or antagonistic activity *in vitro* depending upon the molar ratios of the agents tested. The relationship between *in vitro* susceptibility of HIV to stavudine and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced susceptibility to stavudine have been selected *in vitro* and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV isolates from stavudine-treated patients revealed, in 3 of 20 paired isolates, a 4- to 12-fold decrease in susceptibility to stavudine *in vitro*. The genetic basis for these susceptibility changes has not been identified. The clinical relevance of changes in stavudine susceptibility has not been established.

Cross-resistance: Five of 11 stavudine post-treatment isolates developed moderate resistance to zidovudine (9- to 176-fold) and 3 of those 11 isolates developed moderate resistance to didanosine (7- to 29-fold). The clinical relevance of these findings is unknown.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (Table 1). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption: Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution.

Distribution: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 $\mu g/mL$. Stavudine distributes equally between red blood cells and plasma.

Metabolism: The metabolic fate of stavudine has not been elucidated in humans.

Excretion: Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

Parameter	Adult Patients	n	Pediatric Patients	n
Oral bioavailability (F)	$86.4 \pm 18.2\%$	25	$76.9 \pm 31.7\%$	20
Volume of distribution ^a (VD)	58 ± 21 L	44	18.5 ± 9.2 L/m ²	21
Apparent oral volume of distribution ^b (VD/F)	66 ± 22 L	71	not determined	-
Ratio of CSF: plasma concentrations (as %) ^c	not determined	-	$59 \pm 35\%$	8
Total body clearance ^c (CL)	8.3 ± 2.3 mL/min/kg	44	247 ± 94 mL/min/m ²	21
Apparent oral clearance ^c (CL/F)	8.0 ± 2.6 mL/min/kg	113	333 ± 87 mL/min/m ²	20
Elimination half-life ($T_{1/2}$), I.V. dose ^a	1.15 ± 0.35 h	44	1.11 ± 0.28 h	21
Elimination half-life ($T_{1/2}$), oral dose ^b	1.44 ± 0.30 h	115	0.96 ± 0.26 h	20
Urinary recovery of stavudine (% of dose)	$39 \pm 23\%$	88	$34 \pm 16\%$	19

^a following 1 hour I.V. infusion

^b following single oral dose

^c following multiple oral doses

Special Populations:

Pediatric: For pharmacokinetic properties of stavudine in pediatric patients, see Table 1.

Renal Insufficiency: Data from two studies indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 2). C_{max} and T_{max} were not significantly altered by renal insufficiency. The mean \pm SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min ($n=12$); the mean \pm SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2-6 hours post-dose, was $31 \pm 5\%$. Based on these observations, it is recommended that ZERIT (stavudine) dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see DOSAGE AND ADMINISTRATION).

	Creatinine Clearance			
	>50 mL/min (n=10)	26-50 mL/min (n=5)	9-25 mL/min (n=5)	Hemodialysis Patients* (n=11)
CL _{cr} (mL/min)	104 ± 28	41 ± 5	17 ± 3	NA
CL/F (mL/min)	335 ± 57	191 ± 39	116 ± 25	105 ± 17
CL _R (mL/min)	167 ± 65	73 ± 18	17 ± 3	NA
$T_{1/2}$ (h)	1.7 ± 0.4	3.5 ± 2.5	4.6 ± 0.9	5.4 ± 1.4

CL_{cr} = creatinine clearance

CL/F = apparent oral clearance

CL_R = renal clearance

$T_{1/2}$ = terminal elimination half-life

NA = not applicable

*Determined while patients were off dialysis.

Hepatic Insufficiency: Stavudine pharmacokinetics were not altered in 5 non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Geriatric: Stavudine pharmacokinetics have not been studied in patients >65 years of age. (See PRECAUTIONS: Geriatric Use.)

Gender: A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males ($n=291$) and females ($n=27$).

Race: A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients (233 Caucasian, 39 African American, 41 Hispanic, 1 Asian, and 4 Other). The results of this analysis showed no clinically important differences associated with race.

Drug Interactions: Drug interaction studies have demonstrated that there are no clinically significant interactions between stavudine and the following: didanosine, lamivudine, or nevirapine.

Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT is not recommended.

INDICATIONS AND USAGE

ZERIT, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (see CLINICAL STUDIES).

CLINICAL STUDIES

Combination Therapy: The combination use of ZERIT is based on the results of clinical studies in HIV-infected patients in double- and triple-combination regimens with other antiretroviral agents.

One of these studies (START 1) was a multicenter, randomized, open-label study comparing ZERIT (40 mg twice daily) plus lamivudine plus indinavir to zidovudine plus lamivudine plus indinavir in 202 treatment-naïve patients. Both regimens resulted in a similar magnitude of inhibition of HIV RNA levels and increases in CD4 cell counts through 48 weeks.

Monotherapy: The efficacy of ZERIT was demonstrated in a randomized, double-blind study (A1455-019, conducted 1992-1994) comparing ZERIT with zidovudine in 822 patients with a spectrum of HIV-related symptoms. The outcome in terms of progression of HIV disease and death was similar for both drugs.

CONTRAINDICATIONS

ZERIT is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS

1. Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. In addition, deaths attributed to hepatotoxicity have occurred in patients receiving the combination of ZERIT, didanosine, and hydroxyurea.

Particular caution should be exercised when administering ZERIT to any patient with known risk factors for liver disease; however, cases have also

been reported in patients with no known risk factors. Treatment with ZERIT (stavudine) should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea compared to when ZERIT is used alone. Patients treated with this combination should be closely monitored for signs of liver toxicity.

2. Peripheral Neuropathy: Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving ZERIT therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see ADVERSE REACTIONS).

3. Pancreatitis: Fatal and nonfatal pancreatitis have occurred during therapy when ZERIT was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. The combination of ZERIT and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of ZERIT after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS

Information for Patients (see Patient Information Leaflet): Patients should be informed that an important toxicity of ZERIT is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of ZERIT may be required if toxicity develops.

Caregivers of young children receiving ZERIT therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Patients should be informed that when ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Patients should be informed that ZERIT is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using ZERIT. They should be advised that ZERIT therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of ZERIT are unknown at this time.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

Drug Interactions: Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT is not recommended. (See CLINICAL PHARMACOLOGY.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 $\mu g/mL$, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 $\mu g/mL$, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days.

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

Pregnancy: Pregnancy "Category C": Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, stavudine should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to stavudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving ZERIT.

Pediatric Use: Use of stavudine in pediatric patients is supported by evidence from adequate and well-controlled studies of stavudine in adults with additional pharmacokinetic and safety data in pediatric patients.

Adverse events that were reported to occur in 105 pediatric patients receiving ZERIT 2 mg/kg/day for a median of 6.4 months in study ACTG 240 were generally similar to those reported in adults.

Stavudine pharmacokinetics have been evaluated in 25 HIV-infected pediatric patients ranging in age from 5 weeks to 15 years and in weight from 2 to 43 kg after I.V. or oral administration of single doses and twice daily regimens (see CLINICAL PHARMACOLOGY, Table 1).

Geriatric Use: Clinical studies of ZERIT (stavudine) did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Greater sensitivity of some older individuals to the effects of ZERIT cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ZERIT is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see **DOSAGE AND ADMINISTRATION: Dosage Adjustment**).

ADVERSE REACTIONS

Adults: ZERIT therapy has been associated with peripheral neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with neurotoxic drug therapy, including didanosine, in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose (see **DOSAGE AND ADMINISTRATION**). If neuropathy recurs after resumption of ZERIT, permanent discontinuation of ZERIT should be considered.

When ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with ZERIT in combination with didanosine and hydroxyurea (see **WARNINGS** and **PRECAUTIONS**).

Selected clinical adverse events that occurred in adult patients receiving ZERIT in a controlled monotherapy study (Study AI455-019) are provided in Table 3.

Table 3 Selected Clinical Adverse Events in Study AI455-019 ^a (Monotherapy)		
Adverse Events	Percent (%)	
	ZERIT (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44
^a Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.		

Pancreatitis was observed in three of the 412 adult patients who received ZERIT in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral naïve adult patients receiving ZERIT from two controlled combination studies are provided in Table 4.

Table 4 Selected Clinical Adverse Events in START 1 and START 2 ^a Studies (Combination Therapy)				
Adverse Events	Percent (%)			
	START 1		START 2	
	ZERIT+ lamivudine+ indinavir (n=100 ^b)	zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine+ indinavir (n=102 ^b)	zidovudine+ lamivudine+ indinavir (n=103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10
^a START 2 compared two triple-combination regimens in 205 treatment-naïve patients. Patients received either ZERIT (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.				
^b Duration of stavudine therapy = 48 weeks.				

Pancreatitis resulting in death was observed in patients treated with ZERIT plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 5.

Table 5 Selected Adult Laboratory Abnormalities in Study AI455-019 ^{a,b}		
Parameter	Percent (%)	
	ZERIT (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13
^a Data presented for patients for whom laboratory evaluations were performed.		
^b Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.		
ULN = upper limit of normal.		

Selected laboratory abnormalities reported in two controlled combination studies are provided in Table 6 and Table 7.

Table 6 Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3-4)				
Parameter	Percent (%)			
	START 1		START 2	
	ZERIT+ lamivudine+ indinavir (n=100)	zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin (>2.6 x ULN)	7	6	16	8
SGOT (AST) (>5 x ULN)	5	2	7	7
SGPT (ALT) (>5 x ULN)	6	2	8	5
GGT (>5 x ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2
ULN = upper limit of normal.				

Table 7 Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)				
Parameter	Percent (%)			
	START 1		START 2	
	ZERIT+ lamivudine+ indinavir (n=100)	zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Total Bilirubin	65	60	68	55
SGOT (AST)	42	20	53	20
SGPT (ALT)	40	20	50	18
GGT	15	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

Observed During Clinical Practice: The following events have been identified during post-approval use of ZERIT (stavudine). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to ZERIT, or a combination of these factors.

Body as a Whole- abdominal pain, allergic reaction, and chills/fever.

Digestive Disorders- anorexia.

Exocrine Gland Disorders- pancreatitis [including fatal cases

(see **WARNINGS**)].

Hematologic Disorders- anemia, leukopenia, and thrombocytopenia.

Liver- lactic acidosis and hepatic steatosis (see **WARNINGS**), hepatitis and liver failure.

Musculoskeletal- myalgia.

Nervous- insomnia.

Pediatric Patients: Adverse reactions and serious laboratory abnormalities in pediatric patients were similar in type and frequency to those seen in adult patients.

OVERDOSAGE

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean ±SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

DOSAGE AND ADMINISTRATION

The interval between doses of ZERIT should be 12 hours. ZERIT may be taken without regard to meals.

Adults: The recommended dose based on body weight is as follows:
40 mg twice daily for patients ≥60 kg.
30 mg twice daily for patients <60 kg.

Pediatrics: The recommended dose for pediatric patients weighing less than 30 kg is 1 mg/kg/dose, given every 12 hours. Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.

Dosage Adjustment: Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. These symptoms may be difficult to detect in young children (see **WARNINGS**). If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose.

20 mg twice daily for patients ≥60 kg.
15 mg twice daily for patients <60 kg.

If neuropathy recurs after resumption of ZERIT, permanent discontinuation of ZERIT should be considered.

Renal Impairment- ZERIT may be administered to adult patients with impaired renal function with adjustment in dose as shown in Table 8.

Table 8 Recommended Dosage Adjustment for Renal Impairment		
Creatinine Clearance (mL/min)	Recommended ZERIT Dose by Patient Weight	
	≥60 kg	<60 kg
>50	40 mg every 12 hours	30 mg every 12 hours
26-50	20 mg every 12 hours	15 mg every 12 hours
10-25	20 mg every 24 hours	15 mg every 24 hours

Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of ZERIT in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis Patients- The recommended dose is 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on non-dialysis days.

Method of Preparation:

ZERIT for Oral Solution

Prior to dispensing, the pharmacist must constitute the dry powder with purified water to a concentration of 1 mg stavudine per mL of solution, as follows:

1. Add 202 mL of purified water to the container.
2. Shake container vigorously until the powder dissolves completely. Constitution in this way produces 200 mL (deliverable volume) of 1 mg/mL stavudine solution. The solution may appear slightly hazy.
3. Dispense solution in original container with measuring cup provided. Instruct patient to shake the container vigorously prior to measuring each dose and to store the tightly closed container in a refrigerator, 36° to 46°F (2° to 8°C). Discard any unused portion after 30 days.

HOW SUPPLIED

ZERIT® (stavudine) Capsules are available in the following strengths and configurations of plastic bottles with child-resistant closures:


Table 9				
Product Strength	Capsule Shell Color	Markings on Capsule (in Black Ink)	Capsules per Bottle	NDC No.
15 mg	Light yellow & dark red	BMS 1964 15	60	0003-1964-01
20 mg	Light brown	BMS 1965 20	60	0003-1965-01
30 mg	Light orange & dark orange	BMS 1966 30	60	0003-1966-01
40 mg	Dark orange	BMS 1967 40	60	0003-1967-01

ZERIT® (stavudine) for Oral Solution is a dye-free, fruit-flavored powder that provides 1 mg of stavudine per mL of solution upon constitution with water. Directions for solution preparation are included on the product label and in the **DOSAGE AND ADMINISTRATION** section of this insert. ZERIT for Oral Solution (NDC No. 0003-1968-01) is available in child-resistant containers that provide 200 mL of solution after constitution with water.

US Patent No.: 4,978,655

Storage: ZERIT Capsules should be stored in tightly closed containers at controlled room temperature, 59° to 86°F (15° to 30°C).

ZERIT (stavudine) for Oral Solution should be protected from excessive moisture and stored in tightly closed containers at controlled room temperature, 59° to 86°F (15° to 30°C). After constitution, store tightly closed containers of ZERIT for Oral Solution in a refrigerator, 36° to 46°F (2° to 8°C). Discard any unused portion after 30 days.



Bristol-Myers Squibb Company
Princeton, NJ 08543
U.S.A.

F9-B001-10-00
J4673A
Printed USA

1099813A1
1967DIM-3
Revised August 2000

PATIENT INFORMATION
ZERIT®
(generic name = stavudine, also known as d4T)

ZERIT® (stavudine) Capsules
ZERIT® (stavudine) for Oral Solution

What is ZERIT?

ZERIT (pronounced ZER it) is a prescription medicine used in combination with other drugs to treat adults and children who are infected with HIV (the human immunodeficiency virus), the virus that causes AIDS. ZERIT belongs to a class of drugs called nucleoside analogues. By reducing the growth of HIV, ZERIT helps your body maintain its supply of CD4 cells, which are important for fighting HIV and other infections.

ZERIT will not cure your HIV infection. At present there is no cure for HIV infection. Even while taking ZERIT, you may continue to have HIV-related illnesses, including infections caused by other disease-producing organisms. Continue to see your doctor regularly and report any medical problems that occur.

ZERIT does not prevent a patient infected with HIV from passing the virus to other people. To protect others, you must continue to practice safe sex and take precautions to prevent others from coming in contact with your blood and other body fluids.

There is limited information on the long-term use of ZERIT.

Who should not take ZERIT?

Do not take ZERIT if you are allergic to any of its ingredients, including its active ingredient, stavudine, and the inactive ingredients. (See **Inactive Ingredients** at the end of this leaflet.) Tell your doctor if you think you have had an allergic reaction to any of these ingredients.

How should I take ZERIT? How should I store it?

Your doctor will determine your dose (the amount in each capsule or spoonful) based on your body weight, kidney and liver function, and any side effects that you may have had with other medicines. Take ZERIT exactly as instructed. Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. ZERIT may be taken with food or on an empty stomach.

Capsules: ZERIT capsules are usually taken twice a day (every 12 hours). Store ZERIT capsules in a tightly closed container at room temperature away from heat and out of the reach of children and pets. Do NOT store this medicine in a damp place such as a bathroom medicine cabinet or near the kitchen sink.

Oral solution (for children): ZERIT for Oral Solution is taken twice a day (every 12 hours). If your child will be taking ZERIT, the doctor should give you written instructions on how to give this medicine. Before measuring each dose, shake the bottle well. Store ZERIT for Oral Solution in a tightly closed container in a refrigerator and throw away any unused portion after 30 days.

If you have a kidney problem: If your kidneys are not working properly, your doctor may monitor your kidney function while you take ZERIT. Also, your dosage of ZERIT may be adjusted.

What should I do if someone takes an overdose of ZERIT (stavudine)?
If you suspect that someone has taken an overdose of ZERIT, get medical help right away. Contact their doctor or a poison control center.

What should I avoid while taking ZERIT?

Other medicines. Other medicines, including those you can buy without a prescription, may interfere with the actions of ZERIT. You should not use ZERIT in combination with zidovudine (AZT). **Do not take any medicine, vitamin, supplement, or other health preparation without first checking with your doctor.** (Taking ZERIT with other drugs that also may cause peripheral neuropathy may increase your risk of getting this serious side effect.)

Pregnancy: It is not known if ZERIT can harm a human fetus, so ZERIT should be used during pregnancy only after discussion with your doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking ZERIT.**

Nursing: Because studies have shown ZERIT is in the breast milk of animals receiving the drug, it may be present in human breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers **not** breast-feed to reduce the risk of passing HIV infection to their babies and the potential for serious adverse reactions in nursing infants. Therefore, do not nurse a baby while taking ZERIT.

What are the possible side effects of ZERIT?

Serious side effects of ZERIT may include:

- **Lactic acidosis**, severe increase of lactic acid in the blood, **severe liver enlargement**, including inflammation (pain and swelling) of the liver, and **liver failure**, which can cause death.
- **Peripheral neuropathy**, a nerve disorder of the hands and feet.

People who take ZERIT along with other medicines that may cause similar side effects may have a higher chance of developing these side effects than if they took ZERIT alone. For example, if you use ZERIT in combination with other drugs (including didanosine, with or without hydroxyurea) that may be associated with liver enlargement, peripheral neuropathy, or pancreatitis, you may be at increased risk for these side effects. Children experience side effects that are similar to those experienced by adults.

Lactic acidosis and severe liver enlargement: Lactic acidosis and severe liver enlargement, including deaths, have been reported among patients taking ZERIT. The symptoms that may indicate a liver problem may include:

- feeling very weak, tired, or uncomfortable,
- unusual or unexpected stomach discomfort,
- feeling cold,
- feeling dizzy or lightheaded,
- suddenly developing a slow or irregular heartbeat.

If you notice these symptoms or if your medical condition has suddenly changed, stop taking ZERIT and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital. Women, overweight patients, and those who have had lengthy treatment with nucleoside medicines are more likely to develop lactic acidosis. Your doctor should check your liver function periodically while you are taking ZERIT, especially if you have a history of heavy alcohol use or a liver problem. The combination of ZERIT, didanosine, and hydroxyurea may increase your risk for liver damage, which may be fatal. Your doctor should closely monitor your liver function if you are taking this combination.

Peripheral neuropathy: This nerve disorder is rare, but may be serious. **Tell your doctor right away if you or a child taking ZERIT has continuing numbness, tingling, burning, or pain in the feet and/or hands.** A child may not recognize these symptoms or know to tell you that his or her feet or hands are numb, burning, tingling, or painful. Ask your child's doctor for instructions on how to find out if your child develops peripheral neuropathy.

Let your doctor know if you or a child taking ZERIT has ever had peripheral neuropathy, because this condition occurs more often in patients who have had it previously. Peripheral neuropathy is also more likely to occur in patients taking drugs that affect the nerves and in patients with advanced HIV disease, but it can occur at any disease stage. If you develop peripheral neuropathy, your doctor may tell you to stop taking ZERIT. In some cases the symptoms worsen for a short time before getting better. Once symptoms of peripheral neuropathy go away completely, ZERIT may be started again at a lower dose.

Pancreatitis: Pancreatitis is a dangerous inflammation of the pancreas. It may cause death. **Tell your doctor right away if you develop stomach pain, nausea, or vomiting. These can be signs of pancreatitis.** Let your doctor know if you have ever had pancreatitis, regularly drink alcoholic beverages, or have gallstones. Pancreatitis occurs more often in patients with these conditions. It is also more likely in people with advanced HIV disease, but can occur at any disease stage. The combination of ZERIT and didanosine, with or without hydroxyurea, may increase your risk for pancreatitis.

Other side effects: In addition to peripheral neuropathy, the most frequent side effects observed in studies of adults taking the recommended dose of ZERIT were headache, diarrhea, rash, and nausea and vomiting. Other side effects may include abdominal pain, muscle pain, insomnia, loss of appetite, chills or fever, allergic reactions, and blood disorders.

What else should I know about ZERIT?

If you have diabetes mellitus: ZERIT for Oral Solution contains 50 mg of sucrose (sugar) per mL.

Inactive Ingredients:


ZERIT Capsules: microcrystalline cellulose, sodium starch glycolate, lactose (milk sugar), and magnesium stearate in a hard gelatin shell.

ZERIT for Oral Solution: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose (table sugar), and flavoring agents.

This medicine was prescribed for your particular condition. Do not use ZERIT for another condition or give it to others. Keep ZERIT and all other medicines out of the reach of children. Throw away ZERIT when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

This summary does not include everything there is to know about ZERIT. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about ZERIT, your physician and pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.



 Bristol-Myers Squibb Company
Princeton, NJ 08543
U.S.A.

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.